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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,190	10/31/2003	Barbara Grimpe	CWRU-P01-018	1183

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,190	GRIMPE ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *4, 7, 10-11, 14-16, 21-22, 35, 37-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8,9,12,13,17-20,23-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/04; 2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Examiner acknowledges the election, without traverse, of Group I directed to a methods of reducing GAG content in a glial scar and methods of promoting neuronal regeneration and methods of screening agents, in the reply filed on 6 September 2006. The examiner also acknowledges the election of the species of agent of DNA enzymes. The examiner also acknowledges the election of species SEQ ID NOs: 33, 17, and 13. The examiner also acknowledges the election of species Nerve Growth Factor.

Upon review of the species elections, it seems that SEQ ID NO:13 and 17 are not drawn to DNA enzymes and consequently will not be examined. In addition, because DNA enzymes was elected, the base claim(s) will be examined to the extent that it reads on this election.

Claim Status

Claims 1-54 are pending. However, claims 4, 7, 10-11, 14-16, 21-22, 35, 37-54 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-3, 5-6, 8-9, 12-13, 17-20, 23-34, and 36 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The new oath or declaration, having the signatures of all inventors, received on 8 April 2004 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 14 February 2005 and 4 March 2004 consisting of 7 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit from provisional U.S. Application No. 60/423,082 filed 1 November 2002 and claims benefit from provisional U.S. Application No. 60/471,447 filed 16 May 2003. The instant application has been granted the benefit date, 1 November 2002 from the application 60/423,082.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-3, 5-6, 8-9, 12-13, 17-20, 23-34, and 36 provides for a method of reducing GAG content in a glial scar comprising inhibiting one or more of the following, but the claim does not set forth any steps involved in the method/process. The most generic claims (1-3, 17-18, 29-34, 36) do not recite specific active steps. While Claims 5-6, 8-9, 12-13, 19-20, 23-28, include what is administered (agent), they do not recite the subject of the administration or the location of administration.

Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-6, 8-9, 12-13, 17-20, 23-34, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods of reducing GAG content in a glial scar, promoting neuronal regeneration, screening agents, does not reasonably provide enablement for corresponding *in vivo*

methods. In addition, the claims are rejected, because the specification while being enabling for intrathecal and topical administration, does not reasonably provide enablement for other methods of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

Nature of the Invention

The full scope of the claimed invention encompasses *in vivo* delivery of nucleic acids which encode for DNA enzymes. Essentially, this aspect of the claimed invention is a form of gene therapy.

Working Examples and Guidance Provided

The instant specification described *in vitro* studies of DNA enzymes (examples 6-7). Example 8 describes *in vivo* administration to spinal injuries in mice of Xylotransferase (XT-1) DNA enzyme via intrathecal administration using an osmotic minipump. Histological analysis of the treated areas indicated some neuroregeneration. Beyond Example 8, there is no further guidance given in regard to alternative delivery methods, dosing, or targeting of the vectors expressing the DNA enzyme. Furthermore, the mouse experiments were terminated before any clinical benefit was shown. Because of the difficulties intrinsic to methods of neuroregeneration, the standard for enablement requires support for recovery of function. The examples in the instant application fail to whether there was clinical benefit to the animals treated.

State of the Art and Analysis of the Issues

The nature of the invention being gene therapy, the state of the prior art is not well developed and is highly unpredictable. Verma et al (Nat. 1997 Sep; 389:239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine

experimentation. Eck et al. (Phar Basis Ther 1996; 77-101) explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of DNA enzyme produced, the stability of the DNA enzyme produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. (paragraph bridging pages 81-82) Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3).

In particular, treatments for spinal cord injuries are fraught with difficulties. "Translation of promising results obtained in animal experiments to a possible beneficial effect in humans is still difficult." (Dijkhuizen et al. Neurosci. Res. Comm. Vol.24, No.1; (1998). page 8). The delivery issue is complicated by the blood barrier, "delivery of...factors to... the injured spinal cord is notoriously difficult, since these...do not cross the blood brain barrier." (Dijkhuizen et al., page 1). Dijkhuizen et al. also describe a number of the difficulties of applying gene therapy approaches to neurons (pages 7-8), including immune response directed against neuronal cells, and neuronal cell death. Of course, the goal of all such research, "Translation of promising results obtained in

animal experiments to a possible beneficial effect in humans is still difficult. " (Dijkhuizen et al. page 8).

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require undue experimentation to practice the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2 and 5-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Grimpe et al (The Journal of Neuroscience, April 15, 2002, 22(8):3144–3160).

Claim 1 is directed to a method of reducing GAG content in a glial scar comprising inhibiting one or more of the following: inhibiting the expression of primary proteoglycans; inhibiting the expression and/or activity of a chain initiation enzyme; and inhibiting the expression and/or activity of a chain elongation enzyme.

Grimpe et al. teach indirect reduction of proteoglycan content in a glial scar "reduction of laminin expression by using...DNA enzyme technology" and "the loss of

laminin could affect indirectly the function of other molecules. Laminin is known to bind to...proteoglycans" (page 3158, column 1).

Claim 2 is directed to the further limitation of proteoglycans being neurocan, NG2 or phosphocan. Grimpe et al. teach the proteoglycans "neurocan". (page 3151, column 2).

Claim 5 is directed to expression of the primary proteoglycan is inhibited by administering an agent. Grimpe et al. teach "reduction of laminin expression by using...DNA enzyme technology" and "the loss of laminin could affect indirectly the function of other molecules. Laminin is known to bind to...proteoglycans" (page 3158, column 1). Because laminin expression is reduced by a DNAzyme agent, and proteoglycans are associated with laminin, the expression of proteoglycans is likewise reduced.

Claim 6 is directed to the agent is DNA enzyme. Grimpe et al teach "DNA enzyme technology" (page 3158, column 1).

Accordingly, Grimpe et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-6, 8-9, 12, 17-20, 23, 25-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al. (Nature. (11 April 2002). 416: 636-640) in view of Santoro et al. (*PNAS. 1997; 94:* 4262-4266) and further in view of Götting et al. (J.Mol.Biol. 2000; 304: 517-528) and further in view of Marchetti (Frontiers in Bioscience 2 d. 88-125, March 1, 1997).

Claim 1 is directed to a method of reducing GAG content in a glial scar comprising inhibiting one or more of the following: inhibiting the expression of primary proteoglycans; inhibiting the expression and/or activity of a chain initiation enzyme; and inhibiting the expression and/or activity of a chain elongation enzyme.

Bradbury et al. teach a method in a "glial scar...degrading chondroitin sulphate (CS)-GAG after spinal cord injury" (page 636) in a "glial scar" (page 636). If the GAG is

degraded, it is necessarily reduced in content. Because the specification does not define the phrase "inhibiting the expression of primary proteoglycans", the phrase is being given the broadest reasonable interpretation. Given this interpretation, Bradbury teaches the limitation of "inhibiting expression of primary proteoglycans"

Claim 2 is directed to primary proteoglycans are neurocan, phosphacan and NG2. Bradbury et al teach "neurocan, phosphacan and NG2" (page 639).

Claim 5 is directed to expression of the primary proteoglycan is inhibited by administering an agent. Bradbury et al. teach "Removing CSPG glycosaminoglycan (GAG) chains attenuates CSPG inhibitory activity" (page 636) and "chondroitinase ABC (ChABC)...degraded CS-GAG at the injury site" (page 636). In this case, the ChABC is an agent.

Claim 3 is directed to inhibiting chain initiation enzyme, xylotransferase. Claim 6 is directed to DNA enzymes. Claim 8 is directed to inhibiting expression and/or activity of chain initiation enzyme by administering agent. Claims 9, 12 and 32 are directed to the agent is a DNA enzyme. Claim 17-20 and 23 are directed to promoting neuronal regeneration by inhibiting a chain initiation enzyme, and specifically xylotransferase, by administering an agent that is a DNA enzyme. Claim 25 is directed to the further limitation of claim 17 comprising administering a neurotrophic factor.

The teachings of Bradbury et al. are described above. Bradbury et al. does not teach DNA enzymes or specifically a DNA enzyme which inhibits the chain initiation enzyme, xylotransferase. In addition to the teachings described above, Bradbury et al. teach "other treatments...neurotrophic factor" (page 639)

Santoro et al teach "DNA enzyme can be made to target...to cleave...mRNA" (page 4264, abstract). Santoro et al. also teach DNA enzymes " inactivate target cellular RNAs," (page 4266). Combining these teachings with those of Bradbury et al. satisfies claim 6. Santoro et al. further teach screening a "library" (page 4264).

Götting et al. teach "β-D-xylosyltransferase...initiates the biosynthesis of glycosaminoglycan chains in proteoglycans" (page 517, abstract). Combining this teaching with those of Bradbury et al. and Santoro et al. satisfies the limitations of claims 3, 6, 8-9, 12, 17-20, 23, 25 and 32-33.

Claims 26-28 are directed to the further limitations of claim 25, growth factor or neurotropic factor is nerve growth factor (claim 26), basic Fibroblast Growth Factor (bFGF) (claim 27), and proteoglycans specific enzyme (claim 28).

Marchetti teaches, "Nerve Growth factor" (page 93) and "basic fibroblast growth factor" (page 93) and "bFGF...bind to proteoglycans" (page 92). Combining this teaching with those of Bradbury et al. and Santoro et al. and Götting et al. satisfies the limitations of claims 26-28.

Claims 29-31 are directed to a methods of screening to identify and/or characterize an agent, wherein said agent is capable of one or more of the following: (i) inhibiting the expression of a primary proteoglycan; (ii) inhibiting the expression and/or activity of a chain initiation enzyme; (iii) inhibiting the expression and/or activity of a chain elongation enzyme; or (iv) inhibiting the expression and/or activity of a chain sulfation enzyme, (v) reducing scar formation; (vi) promoting inter-mixing of Schwann cells and astrocytes; or (vii) promoting neuronal regeneration and/or intermixing of

schwann cells and astrocytes. Bradbury et al teach the further limitations of methods "to test...chondroitinase ABC (ChABC)" which "promoted regeneration...axons" (page 636).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to reduce GAG content in glial scars and promote neuronal regeneration by inhibiting proteoglycans and specifically GAG initiation through DNA enzyme inactivation of xylotransferase.

The person of ordinary skill in the art would have been motivated to make those modifications because (chondroitin sulphate proteoglycans) "CSPGs are important inhibitory molecules in vivo and suggest that their manipulation will be useful for treatment of human spinal injuries" (Bradbury et al., page 636-637) and "β-D-xylosyltransferase...initiates the biosynthesis of glycosaminoglycan chains in proteoglycans" (Götting et al., page 517, abstract). Together Bradbury and Götting suggest the obvious target of xylotransferase for inhibition of GAG content in glial scars and promotion of neuronal regeneration. Furthermore, "The 10-23 DNA enzyme can be made to cleave almost any target....are inexpensive and readily obtainable. A more intriguing possibility is that it could be used to inactivate target cellular RNAs" (Santoro et al. page 4266). When considering Santoro's teachings on DNA enzymes, in light of the target suggested by Bradbury and Götting, it makes the choice of DNA enzymes as an inhibitor seem straightforward. The Marchetti reference merely identifies species of molecules that could augment the recommended method of Bradbury et al. in view of Santoro et al. and further in view of Götting et al.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Bradbury et al. and Santoro et al. and Götting et al. because at the time of the instant invention, (1) DNA enzymes had been successfully used as inhibitors of gene expression and (2) inhibiting proteoglycans in the intracellular matrix around glial scars was known to reduce GAG content and promote neuronal regeneration.

Therefore the method as taught by Bradbury et al. in view of Santoro et al. and further in view of Götting et al. and further in view of Marchetti would have been *prima facie* obvious over the method of the instant application.

Claim 34 is rejected under 35 U.S.C. 103(a) as being obvious Bradbury et al. in view of Santoro et al. and further in view of Götting et al. and further in view of Marchetti

None of the references teach a pharmaceutical preparation of the agent.

However, it would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make a pharmaceutical preparation of an active ingredient.

The person of ordinary skill in the art would have been motivated to make a pharmaceutical preparation of the agent, because this is common, if not required for use as a therapy.

An artisan would have expected success, because making pharmaceutical preparations have been performed for an extremely long time. Pharmaceutical preparations of DNA have also been make for many years.

Therefore the method as taught by Bradbury et al. in view of Santoro et al. and further in view of Götting et al. and further in view of Marchetti would have been *prima facie* obvious over the method of the instant application.

Claim 36 is rejected under 35 U.S.C. 103(a) as being obvious Bradbury et al. in view of Santoro et al. and further in view of Götting et al. and further in view of Marchetti

None of the references teach methods of packaging, marketing, and selling the pharmaceutical preparation.

However, it would have been obvious to the person of ordinary skill in the art at the time of the invention was apply these business practices a pharmaceutical preparation of an active ingredient (agent).

The person of ordinary skill in the art would have been motivated to apply these business practices to pharmaceutical preparation of the agent, because this is common, even necessary in the standard practices of the pharmaceutical industry.

An artisan would have expected success, because applying these business practices have been performed in the pharmaceutical industry for a long time.

Therefore the method as taught by Bradbury et al. in view of Santoro et al. and further in view of Götting et al. and further in view of Marchetti would have been *prima facie* obvious over the method of the instant application.

Conclusion

No Claims are allowed. However, SEQ ID NO:33 and 39 are free of the art.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave Nguyen** can be reached on **571-272-0731**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER